

REMARKS

I.      *Status Summary*

Claims 1, 6, and 8 are pending in the present U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over *Cereijido et al.* (1993) Suppl 17 *J Cell Science* 127-132 (hereinafter "Cereijido") in view of *Grunicke et al.* (1996) 36 *Advan Enzyme Regul* 385-407 (hereinafter "Grunicke").

Claims 9-27 have been canceled without prejudice. Applicants hereby respectfully reserve the right to file one or more divisional applications with claims directed to the subject matter of the claims canceled herein.

Reconsideration of the application based on the application as amended and in light of the remarks set forth below is respectfully requested.

II.     *Summary of the Telephone Interview*

A telephone interview was conducted on October 7, 2008 between Examiners Frederick Krass and Benjamin J. Packard of the Patent Office and applicants' representatives Arles A. Taylor, Jr. and Christopher P. Perkins. Discussed during the telephone interview was applicants' contention that with respect to the alkylphosphocholines of certain carbon chain lengths, unexpectedly superior results were demonstrated in the specification for these embodiments relative to the dodecylphosphocholine. The Examiners indicated that they would consider this argument with respect to chain lengths of 14-20 carbons based on the data presented in the specification.

Applicants would like to thank Examiner Krass and Packard for their time and consideration with respect to the telephone interview and the issues discussed, and believe that the instant amendment is consistent with the subject matter of the telephone interview.

III.    *Response to the Obviousness Rejection*

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a), upon the contention that the claims are unpatentable over Cereijido in view of Grunicke. According to the Patent Office, Cereijido teaches that inhibition of phospholipase C reduces the

development of the transepithelial electrical resistance (TER; also abbreviated as TEER), which the Patent Office asserts is a measure for the paracellular transport through cells, and activation of phospholipase C increases TER. Thus, the Patent Office contends that one of ordinary skill in the art would understand *a priori* that phospholipase C plays an important role in paracellular transport across the intestinal epithelium and that upon administration of a phospholipase C inhibitor the paracellular membrane permeability would be enhanced (see Official Action at page 4). The Patent Office further asserts that Grunicke teaches that hexadecylphosphocholine (HePC, Miltefosine, n = 15) is an inhibitor of PI-specific phospholipase C.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

In support of the instant rejection, the Patent Office asserts that Cereijido teaches that inhibition of PLC reduces the development of TER and activation of PLC increases TER. Applicants respectfully submit that these assertions are not supported by the disclosure of Cereijido. Rather, applicants respectfully submit that at best Cereijido suggests that neomycin could inhibit the development of TER and TRH could stimulate the development of TER by inhibiting or stimulating, respectively, the generation of new tight junctions. Applicants respectfully submit that this does not provide one of ordinary skill in the art with a reasonable expectation that either of these chemicals would impact paracellular permeability in already-formed tight junctions.

To this, the Patent Office asserts that the pre-formation of tight junctions is not an element of the instant claims. Applicants respectfully disagree. Applicants respectfully submit that claim 1 recites *inter alia* a method of enhancing paracellular permeability at an absorption site in a subject. Applicants respectfully submit that when one of ordinary skill in the art considers the claims in view of the instant specification as is required under M.P.E.P. § 2111, one of ordinary skill in the art would understand that the tight junctions are already formed at the relevant absorption sites. Thus, applicants respectfully submit that there is no basis for the Patent Office to assert that applicants' arguments have attempted to import a limitation from the specification into the claims.

Turning now to the disclosure of Grunicke, applicants respectfully submit that Grunicke does not cure the deficiencies of Cereijido.

Additionally, while applicants do not acquiesce to the Patent Office's assertion that a *prima facie* case of obviousness has been presented, applicants respectfully submit that claim 1 presently recites carbon chain lengths of 14 to 20 carbons, and the specification

as filed clearly demonstrates that alkylphosphocholines with carbon chain lengths of between 14 and 20 carbons inclusive are unexpectedly superior in their activities when compared to dodecylphosphocholine as disclosed in Cereijido. This information is provided in the specification at page 36 in Table 2. Table 2 directly compares the activities of C12, C14, C16, C18, and C20 alkylphosphocholines. With respect to the inhibitory activities of these various alkylphosphocholines, hexadecylphosphocholine (C12) has an  $IC_{50}$  value of  $275 \pm 135 \mu M$ . C14 alkylphosphocholine, on the other hand, has an  $IC_{50}$  value of  $73 \pm 9 \mu M$ , which means that it is almost 4 times as potent a PCL inhibitor as dodecylphosphocholine. Similarly, the  $IC_{50}$  values for C16, C18, and C20 are even lower than C14:  $36 \pm 18 \mu M$  (C16),  $30 \pm 2 \mu M$  (C18), and  $48 \pm 5 \mu M$  (C20).

Applicants further respectfully submit that the differences between these compounds with respect to  $EC_{50}$  values (*i.e.*, the amount of the inhibitor required to reduce paracellular permeability by 50%; see specification at page 2, Table of Abbreviations) is even more dramatic than the  $IC_{50}$  data. Particularly, the  $EC_{50}$  value of C12 is  $733 \pm 32 \mu M$ . The  $EC_{50}$  values of C14, C16, C18, and C20 are approximately 10- to 25-fold lower ( $44 \pm 11 \mu M$ ,  $29 \pm 5 \mu M$ ,  $59 \pm 8 \mu M$ , and  $71 \pm 8 \mu M$ , respectively). Applicants respectfully submit that the 4- to 9-fold differences in  $IC_{50}$  values and the 10- to 25-fold differences in the  $EC_{50}$  values of the presently disclosed subject matter represents unexpectedly superior results that rebut the Patent Office's asserted *prima facie* case, if made, under M.P.E.P. §§ 2144.09 and 2154.

Summarily, applicants respectfully submit that the claim 1 has been distinguished over the combination of Cereijido and Grunicke. As a result, applicants respectfully request that the instant rejection of claim 1 be withdrawn at this time. Claims 6 and 8 both depend from claim 1, and thus are also believed to be distinguished over the cited references. Applicants further respectfully submit that claims 1, 6, and 8 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect

### CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully

requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

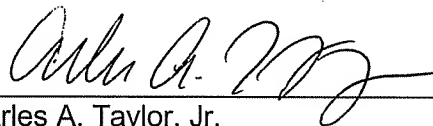
Although no fee is believed to be due with respect to the filing of the instant paper, the Commissioner is hereby authorized to charge any underpayment of fees, and to credit any over payment, to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: November 14, 2008

By: \_\_\_\_\_



Arles A. Taylor, Jr.  
Registration No. 39,395  
Customer No. 25297  
(919) 493-8000

421/32/2      AAT/CP/PP/cam